Amyloid Structural Heterogeneities in Alzheimer's Disease

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Although aggregation of Ab amyloid fibrils into plaques in the brain is a hallmark of Alzheimer's Disease (AD), the correlation between amyloid burden and severity of symptoms is weak. One possible reason is that amyloid fibrils are structurally polymorphic and different polymorphs may contribute differentially to disease. Here, we describe the use of X-ray microdiffraction of histological sections of human tissue to map the abundance, orientation and structural heterogeneities of amyloid within individual plaques; among proximal plaques and in subjects with distinct clinical histories. A 5 m x-ray beam was used to generate diffraction data with each pattern arising from a scattering volume of only ~ 450 m^3, making possible collection of dozens to hundreds of diffraction patterns from a single amyloid plaque. X-ray scattering from these samples exhibited all the properties expected for scattering from amyloid. Margins of plaques exhibited a greater degree of orientation than cores and orientation around blood vessels frequently appeared tangential. The structure of Ab fibrils is reflected in the shape of the 4.7 Å peak which is universally observed in scattering from amyloid. Variations in this peak revealed differences between the structure of amyloid within cores of plaques and at their periphery. We demonstrate the existence of structural polymorphisms among amyloid within and among plaques of a single individual and suggest the existence of distinct differences in the organization of amyloid in subjects with different clinical presentations.